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The remarkable discovery by Reed and his colleagues, at the turn of the present century, that yellow fever is an insect-borne disease, was the first, and the most outstanding, landmark in the long struggle against this dreadful disease. The conclusion of these workers that the agent solely responsible for the transmission of the infection from person to person was the mosquito, *Aëdes (Stegomyia) aegypti,* (L), pointed clearly to the eradication of this insect as the most practical method of eliminating the disease. Sanitarians were quick to accept this principle and put it into practice, and, at the beginning of the period we now have under consideration, successful control campaigns have been completed, or were in progress, in Havana, Veracruz, the Isthmus of Panama, and Rio de Janeiro.

During the next twenty years many successful campaigns were waged against yellow fever, and it is not surprising to find, at an early date, that some of those responsible for planning and directing the work began to foresee the time when the disease would entirely disappear from the Americas. The epidemiological concept upon which the control measures were based was a very simple one. Nevertheless, the experts of the time were satisfied that it took into account all the factors concerned, and it was not until after the lapse of another quarter of a century that its short-comings were brought to light. The concept was based on the belief that man was the only susceptible vertebrate host, and that the mosquito, *Aëdes aegypti,* was the sole vector. The mosquito became infected by feeding on a yellow fever patient during the first three or four days of the illness. Then after an incubation period, the length of which varies with the temperature, the mosquito becomes infective and continues so for the remainder of its life. In this simple man-mosquito-man cycle it is obvious that, for transmission of the disease to continue, there must be an ample supply of the insect vector as well as an adequate number of susceptible individuals. If either of these factors fails, transmission will cease and the outbreak will come to an end. The simplest way in which to bring this about was by attacking the vector. It is a domestic mosquito which

breeds, for the most part, in artificial water containers in and around houses. Breeding can readily be controlled by weekly inspection of these containers, with destruction of larvae when they are found.

It was observed, early in the campaign, that *aegypti* control, in many cities in Central and South America, rapidly led to the disappearance of the disease. Furthermore, it was found that successful control in the large centers was usually accompanied by the suppression of the infection in the surrounding countryside. From this it was concluded that yellow fever could persist only in large cities, where there was an adequate influx of susceptible strangers and new-born children to prevent the disease from burning itself out through failure of the human host. If the vector was controlled in these large cities, or key-centers as they were called, yellow fever should disappear from the community, since outbreaks in all the smaller places were deemed to be secondary, and unable to persist in the absence of the main focus.

Following the original anti-mosquito campaign in Havana, successful control measures were carried out in many places which had been notorious danger spots in subtropical and tropical America. An epidemic in New Orleans in 1905 was quickly brought under control and the United States was not again invaded. Yellow fever gradually vanished from the West Indies, and a successful control campaign was begun in the Amazon basin in 1912. In 1916, the Rockefeller Foundation, which had become actively interested in yellow fever, appointed a commission to make a survey of the situation in South America. In their report they concluded that the only endemic center in South America was in Guayaquil, Ecuador. They recommended that the infection be eliminated from Guayaquil, that the east coast of Brazil and the southern littoral of the Caribbean be kept under observation and that investigations be extended to Mexico and West Africa, both of which regions were under suspicion. They were satisfied that the program should have as its ultimate objective the complete extinction of the disease.

The advent of World War I delayed the initiation of the campaign in Guayaquil, and it was not until 1918 that it again came under consideration. At this time it was deemed advisable to learn more about the disease in Ecuador, and a special commission was appointed to undertake this. Its members included experts in clinical medicine, epidemiology, bacteriology, and chemistry, and they arrived in Guayaquil in July, 1918. A few months later came the startling announcement by Noguchi, the commission bacteriologist, that he had isolated, from patients said to be suffering from yellow fever, a leptospira, which when injected into guinea pigs, produced lesions suggestive of yellow fever. Later, this same organism was isolated by Noguchi, and by other investigators, during yellow fever epidemics in Mexico, Peru and Brazil. In due course, and after much experimental study, Noguchi concluded that this was the causative organism of yellow fever, and he named it *Leptospira icteroides.* Although this conclusion was later proved to be erroneous, it was

soon almost, but not quite, universally accepted. Although the findings of Reed and his associates had been amply confirmed by many workers in many countries, they were overlooked when this new and contradictory evidence was brought forth by a distinguished scientist. The result was to further confuse the issue where the etiology of yellow fever was concerned. Presumably the explanation of the error lies in the fact that, clinically, yellow fever and spirochetal jaundice may closely resemble one another and, in addition, the two diseases are sometimes present at the same time. Undoubtedly, Noguchi isolated the etiological agent of the disease with which he was working, but, unfortunately, that disease was not yellow fever. The episode illustrates very well the ease with which, under certain circumstances, a false scientific deduction may gain general acceptance and be treated as fact until, at some future date, some one reinvestigates and discovers the error. On the other hand the experience of Carlos Finlay illustrates equally well the difficulties which may have to be overcome in getting recognition for a conclusion which is eventually proven to the satisfaction of everyone to have been valid.

In 1918, the Rockefeller Foundation, in collaboration with the Governments of the countries where yellow fever might be found, launched a full-scale campaign for the eradication of the disease from the Western Hemisphere. The first project, which was commenced in Guayaquil, late in 1918, was a conspicuous success, and the city was declared free of the disease in 1920. During the next five years a long series of successful campaigns was carried out in many countries in Central and South America, and, by 1925, it was believed that the only remaining foci of yellow fever in the Western Hemisphere were in a relatively small area of Northeast Brazil. Control measures which were in progress in this area had already yielded promising results. Thus, in a comparatively short space of time success had been achieved, or so it was believed, and yellow fever was about to disappear from the Americas. Optimism reached a new peak and preliminary arrangements were made to tackle the problem in Africa. Unfortunately the events of the next few years brought keen disappointment to those who had convinced themselves that the struggle against yellow fever in the Western Hemisphere was over.

In 1926, there was a sharp increase in the number of cases in several states in Brazil. These were quickly brought under control and a satisfactory explanation was found for their occurrence. However, a more serious setback occurred in 1928, when the disease appeared in epidemic form in Rio de Janeiro for the first time in 20 years. As this city was almost one thousand miles from the known infected area, no satisfactory explanation could be made at the time as to how the disease had been introduced. Following this, cases appeared in numerous places over a wide area in Brazil, and a small epidemic was reported from the interior of Colombia. In the light of these events it gradually came to be realized that there was something wrong and, perhaps, the epidemiology of yellow fever was not quite as simple as had been supposed. The skill and diligence with which this new problem was tackled and

solved is a most interesting feature of the period immediately following that covered in this review.

Let us now direct our attention towards Africa. Although it is now believed that yellow fever may possibly have originated in Africa, it is not known when the disease first made its appearance there. The available information suggests that it was not recognized as a definite entity until late in the eighteenth century, but it seems reasonable to assume that it must have existed much earlier than that. It is known, however, that, since 1778, it has been almost continuously present upon the West Coast of Africa, and there have been few years since that date when the records have failed to comment upon it. During these early times it was believed to be confined to a comparatively narrow strip along the West Coast, which extended from Senegal in the north to the Cameroons in the South. It sometimes invaded short distances into the interior, along certain much-travelled lines of communication, but its presence farther inland in West Africa, or in Central or East Africa, was never detected, or even suspected. Furthermore, it was rarely diagnosed in the African, and it was only when non-Africans, usually called "Europeans," were attacked, with the attendant high mortality, that the alarm was raised and the event made a matter of record. Early expeditions brought back alarming reports of the deadly fever of the coast, which was referred to as "yellow-jack," "Lagos fever," "fever of the Bight of Benin," and other terms usually referable to the district in which it was encountered. It was these reports which were, in large measure, responsible for the West African Coast becoming known as the "white man's grave," an unsavory reputation which it has never entirely lost.

Interest in the yellow fever problem in Africa was renewed and heightened when it became known that it was an insect-borne disease, and during the next twenty-five years repeated commissions were sent to the West Coast to study the situation and report upon it.

In 1910, Sir Rupert Boyce, whose experience in the New Orleans epidemic in 1905, and subsequently in British Honduras and in the West Indies, fitted him to carry out intensive studies of this disease, spent considerable time upon the West Coast. He collected data upon the recurrence of yellow fever in each of the colonies scattered along the coast, and he presented irrefutable evidence that, for more than one hundred years, the coast had never been free from infection. However, there were still those, at home and abroad, who denied the existence of yellow fever in Africa, claiming that the diagnosis had been confused with other tropical diseases. We know now, of course, that this mistaken conception was, at least in part, due to the fact that the disease was much more prevalent than was supposed in the African population, and that this was the source of the sudden and unexplained outbreaks which occurred, from time to time, among the highly susceptible, but very small white population. The disease was rarely recognized in the African

because the great majority of such cases was so mild as to render diagnosis difficult or impossible, and because febrile illness among Africans was rarely brought to the attention of the relatively very few individuals who were competent to make a diagnosis.

The publication of the reports by Boyce led to considerable agitation and much controversy, and, in 1913, the British Government appointed a yellow fever commission to investigate and report on the situation in West Africa. The members of this Commission spent three years in collecting data. They devoted little time to personally investigating the disease, and concerned themselves mainly in reviewing the evidence of others, who had reported the presence of the infection in Africa. In their report they expressed the view that yellow fever had long been present in West Africa, and that it was widely distributed. In 1910 and 1911, it was prevalent over a wide area, and there were epidemics in Freetown, Bathurst, Sekondi, Accra, and elsewhere. In 1913, there were outbreaks in Lagos, Accra, and several smaller places. The alternation of periods of widespread epidemic conditions, with intervals of relative quiescence, so characteristic of yellow fever, was a conspicuous feature of the picture in West Africa. It was during one of these quiescent periods that a Commission was sent to West Africa, in 1920, by the Rockefeller Foundation, to study the problem. No authentic cases were seen, and the Commission was unable to decide whether the African disease, diagnosed as yellow fever, was actually yellow fever, and, if so, whether control measures would be feasible. It was recommended that the report be treated merely as a progress report, and that another Commission be appointed to carry out a more extensive and prolonged study in West Africa.

Accordingly, in 1925, still another Commission was sent to Africa by the Rockefeller Foundation. This group, known as the West African Yellow Fever Commission, was fully equipped to undertake a thorough and comprehensive study. Its primary objective was to determine whether yellow fever in Africa was identical with that seen in South America. Then, as the program developed, it hoped to isolate the causative organism of the African disease, to discover the mode of transmission, and to identify the areas in which it was endemic.

Field studies were commenced late in 1925, and, in the absence of reported cases, an intensive search for the disease in the African population was undertaken in Nigeria and on the Gold Coast. These efforts were successful, in 1926, when an epidemic was discovered in Asamankese, Gold Coast, a town of approximately 5000, situated in the cocoa-belt fifty miles northwest of Accra. It is of interest to note that this was the first large outbreak, exclusively in the native population, ever observed in West Africa. Although the epidemic was on the wane when the study was initiated some fifty cases were seen in which a clinical diagnosis of yellow fever seemed justified. In addition, a large number of persons were observed who were suffering from a mild febrile ill-

ness in which a clinical diagnosis could not be made. Of the fifty cases included in the study, eight were fatal, eleven were classified as severe, and the remainder were placed in the categories of moderately severe and mild. Later in 1926, and during the early months of 1927, similar, though somewhat smaller, epidemics were studied in two other towns on the Gold Coast and an additional sixty cases were added to the total included in the investigation.

These epidemics afforded an excellent opportunity to study the clinical and pathological features of the disease as it occurred in the African. They left no doubt in the minds of the investigators that fatal and severe yellow fever *did* occur in the African, although the impression was gained that the mortality was very much lower than had been reported in epidemics involving Europeans. Furthermore, the evidence indicated that, clinically and pathologically, the disease was the same as that seen in South America. However, repeated attempts to isolate the *Leptospira icteroides,* or any other organism, failed. Blood specimens taken from over sixty cases during the early days of the illness were inoculated into large numbers of guinea-pigs and into larger numbers of tubes of the special medium recommended by Noguchi for the culture of the *L. icteroides.* The results were completely negative. As this evidence accumulated it became more and more evident that *L. icteroides* was not the causative agent of African yellow fever, and that progress in the laboratory could not be expected until a suitable experimental animal was found. The search for a susceptible animal became the problem of prime importance, and included in the numerous species selected for trial was the rhesus monkey.

A shipment of these animals arrived in Accra at about the same time that attention was attracted to a small Gold Coast village, called Kpeve, where two Europeans had suffered mild attacks of an illness clinically resembling yellow fever. An investigation in Kpeve indicated the recent presence of suspect cases, and, on June 30, 1927, a blood specimen was secured from one such case. The patient, whose name was Asibi, was an African laborer aged about 28, and the specimen was taken some thirty-three hours after the onset of the illness. It was taken immediately to the laboratory in Accra and inoculated into a rhesus monkey. The animal developed fever four days later on July 4, and was found moribund and in collapse the following morning. Postmortem examination revealed lesions similar to those seen in human yellow fever. Blood and tissue preparations from this animal were inoculated into other rhesus monkeys and the propagation of the now famous Asibi strain of yellow fever virus began with this experiment.

Although the Asibi strain of virus is, perhaps, the most virulent for rhesus monkeys which has ever been isolated, it is interesting to observe that it had its origin in an exceedingly mild human case. When the donor, Asibi, was first seen, on the evening of June 29th, he stated that the illness had commenced suddenly at 3 a.m. that day. His temperature was 103°F., pulse 96, and he complained of very severe headache and pain in the lower back. He

appeared very ill and prostration was marked. When seen the following morning the temperature was down to 99.9°F., the headache, though still present, was much less severe, and his general appearance was much improved. He made a rapid recovery and returned to work a few days later. This was a case in which the onset, as well as the very early signs and symptoms, was characteristic of classical yellow fever in severe form, but, within a few hours, the patient's natural resistance asserted itself to overcome the infection, and the attack rapidly subsided. However, the Asibi strain of virus, soon after its isolation, was responsible for an accidental infection in one of the scientists engaged on its study in the laboratory, and it produced, in him, a fulminating attack with death in ninety-six hours. We have, in this experience, a clear and adequate explanation of the sudden outbreaks in Europeans, which apparently came from nowhere, and whose obscure origin caused much confusion in the minds of early observers in West Africa.

The problem of a susceptible experimental animal had now been satisfactorily solved, and a new and fruitful era in yellow fever research was opened. This important advance, at a time when the gravity of the yellow fever situation was being more and more appreciated, acted as a stimulus, and research was soon going on in many laboratories in Europe and America, in addition to those in Lagos and Dakar, in West Africa. All these studies resulted in a wealth of new knowledge much of which was directly applicable to the solution of the problems encountered by the observers in the field. It should be mentioned, however, that nothing was discovered which in any way disturbed the fundamental facts established by the Army Commission in Havana, in 1900. That remarkable contribution, by Walter Reed and his collaborators, has stood the test of time, and it will always remain as an outstanding achievement in the annals of scientific research.

The great variety of investigations which was carried out in many places following the discovery of a suitable experimental animal resulted in a mass of new information covering almost all aspects of the yellow fever problem. We will confine ourselves here to some of the more important early results which were of particular interest to the epidemiologist. Since there are, in West Africa, numerous species of the genus *Aëdes,* which resemble *aegypti* very closely in their binomics, it seemed logical to determine whether any of these could transmit yellow fever from one animal host to another in the laboratory. In the first series of experiments, undertaken to settle this point, successful transmission resulted with two species of *Aëdes,* other than *aegypti,* and with one other species of an entirely different genus. Work along these lines was continued both in Africa and in South America, with the result that an ever increasing number of species of mosquitoes was incriminated in both countries. These were, of course, as yet only potential vectors, and the part they played in the epidemiology of yellow fever remained to be determined.

While the search for a susceptible animal was in progress, in 1926 and early in 1927, numerous African monkeys of several different species were inoculated with blood from yellow fever patients. The results were persistently negative; no rise in temperature or other manifestations of the disease followed the inoculations. With the finding of the highly susceptible rhesus monkey this work was discontinued for a time, but it was later resumed with interesting results. In the initial study in this series, attempts were made to infect African monkeys of four different species with yellow fever, both by injection of virulent blood from infected rhesus monkeys, and by the bite of infected *A. aegypti.* None of the animals died or showed signs of illness, but, for a number of days, the virus persisted in the blood of monkeys of three different species, and it could be recovered by injecting their blood into susceptible rhesus. Furthermore, it was found that, in the case of at least two species, the virus could be transmitted from African to rhesus monkeys by *A. aegypti* mosquitoes. Finally, it was shown that, following exposure to yellow fever virus, several species of African monkeys developed specific protective antibodies in their blood, although these were not present before inoculation. This work was continued in Africa and similar studies were made in South America. The result was that a considerable number of species of indigenous monkeys in both countries were found to be susceptible to yellow fever virus, in the sense that they could harbor the virus for several days during which time they were capable of infecting possible insect vectors which fed upon them.

When it became known that vertebrates other than man were susceptible to yellow fever virus, and that mosquitoes other than *Aëdes aegypti* could act as vectors of the infection, the question arose whether the epidemiology of the disease might not be more complex than had been supposed up to this time. In any case, this was the first inkling that there might be factors concerned which had not previously been taken into account.

Another important early development in the laboratory was the elaboration of a highly specific test, known as the protection test, whereby it was possible to demonstrate the life-long immunity possessed by the individual who had recovered from an attack of yellow fever. The blood serum of such a person contains specific neutralizing antibodies, and when it is injected into a rhesus monkey along with virulent virus, the animal is protected and remains well. When a normal serum is used which contains no protective substances, the virus is not neutralized and the animal succumbs to the infection.

The protection test was used in West Africa to gain information on the distribution of the disease. This was necessary since it was soon realized that reported cases of yellow fever in Africa gave no indication of the actual incidence of the disease. The great majority of cases in Africans are never seen or recognized, and, consequently, there was no accurate information on the number of cases which had occurred, or on the extent of the area involved.

Blood samples were collected in various communities and injected into rhesus monkeys along with virulent yellow fever virus. The survival or death of the animal determined whether the serum possessed specific antibodies. If the animal survived, the result was taken to indicate that the donor had suffered an attack of yellow fever at some time during his life. The first survey of this nature was concerned with the examination of 240 sera collected from both children and adults in several of the larger cities in Nigeria. The most striking result was the demonstration of the heavy past incidence of yellow fever as compared with reported cases throughout the area; a result which was amply confirmed when more extensive work along these lines became possible. The early surveys were necessarily limited in extent because the only experimental animal available at that time was expensive and difficult to get in adequate numbers. However, this difficulty was overcome, a few years later, when it was discovered that the monkey could be replaced by the white mouse as the laboratory animal. The immunity survey was then extended to practically all parts of Africa.

In this brief review an effort has been made to outline some of the more important events in the history of yellow fever which occurred during the quarter century following 1905. Special emphasis has been placed on results which seemed of most interest to the epidemiologist, and to those responsible for the control of the disease. For obvious reasons, it has not been possible, at this time, to discuss a host of investigations on other aspects of the problem, many of which yielded significant results. It is hoped, however, that what has been presented will serve to illustrate the great progress made during this era in the long struggle against yellow fever.